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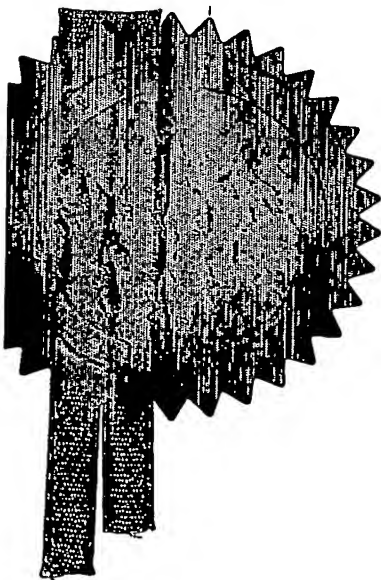
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The Patent Office

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1. Your reference 101078-1 GB

2. Patent application number
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P01/7700 0.00-0314129.8 18 JUN 2003

3. Full name, address and postcode of the or of each applicant (underline all surnames)

AstraZeneca AB
SE-151 85 Sodertalje
Sweden

Patents ADP number (if you know it)

7822448003

If the applicant is a corporate body, give the country/state of its incorporation

Sweden

4. Title of the invention

THERAPEUTIC AGENTS

5. Name of your agent (if you have one)

Thomas Kerr MILLER

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

AstraZeneca UK Limited
Global Intellectual Property
Mereside, Alderley Park
Macclesfield,
Cheshire SK10 4TG

Patents ADP number (if you know it)

7822471002

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Country

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Number of earlier application

Date of filing
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Description 36

Claim(s) 1

Abstract 1

Drawing(s)

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Request for preliminary examination and search (Patents Form 9/77)

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11.

I/We request the grant of a patent on the basis of this application

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Jennifer Bennett - 01625 230148

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Therapeutic AgentsField of the invention

5 The present invention relates to certain novel salts of (2S)-3-(4-(2-[amino]-2-oxoethoxy)phenyl)-2-ethoxypropanoic acid derivatives, to processes for preparing such compounds, to their utility in treating clinical conditions including lipid disorders (dyslipidemias) whether or not associated with insulin resistance and other manifestations of the metabolic syndrome, to methods for their therapeutic use and to pharmaceutical
10 compositions containing them.

Background of the invention

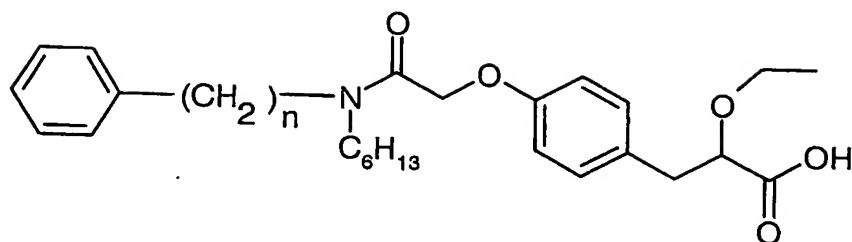
The metabolic syndrome including type 2 diabetes mellitus, refers to a cluster of
15 manifestations including insulin resistance with accompanying hyperinsulinaemia, possibly type 2 diabetes mellitus, arterial hypertension, central (visceral) obesity, dyslipidaemia observed as deranged lipoprotein levels typically characterised by elevated VLDL (very low density lipoproteins), small dense LDL particles and reduced HDL (high density lipoprotein) concentrations and reduced fibrinolysis.

20 Recent epidemiological research has documented that individuals with insulin resistance run a greatly increased risk of cardiovascular morbidity and mortality, notably suffering from myocardial infarction and stroke. In type 2 diabetes mellitus atherosclerosis related conditions cause up to 80% of all deaths.

25 In clinical medicine there is awareness of the need to increase the insulin sensitivity in patients with the metabolic syndrome and thus to correct the dyslipidaemia which is considered to cause the accelerated progress of atherosclerosis. However, currently this is not a universally accepted diagnosis with well-defined pharmacotherapeutic indications.

30 Co-pending PCT application No. PCT/GB02/05743 discloses compounds of formula A

- 2 -



A

wherein n is 1 or 2 and pharmaceutically acceptable salts, solvates, crystalline forms and prodrugs thereof are highly potent PPAR α modulators. PPAR is short peroxisome proliferator-activated receptors (for for a review of the PPARs see T. M. Willson et al , J Med Chem 2000, Vol 43, 527). These compounds are effective in treating conditions associated with insulin resistance. Specific pharmaceutically acceptable salts of compounds of the formula A are not disclosed in PCT/GB02/05743. Further, no information is provided in relation to how crystalline forms of compounds of the formula A, and particularly salts thereof, may be prepared. The compound in which n is 2 is prepared as the free acid in this application. However, this compound is a syrup and is thus not suitable for use in pharmaceutical formulations. Therefore there exists a need for a derivative of this compound which has physical and chemical properties suitable for use in pharmaceutical formulations. Attempts were made to produce salts with many different counter-ions. However, most were unsatisfactory for one of the following reasons. A salt could not be formed in the solid state or if formed the salt was amorphous with a low glass transition temperature.

In the formulation of drug compositions, it is important for the drug substance to be in a form in which it can be conveniently handled and processed. This is of importance, not only from the point of view of obtaining a commercially-viable manufacturing process, but also from the point of view of subsequent manufacture of pharmaceutical formulations comprising the active compound.

Further, in the manufacture of drug compositions, it is important that a reliable, reproducible and constant plasma concentration profile of drug is provided following administration to a patient.

Chemical stability, solid state stability, and "shelf life" of the active ingredients are also very important factors. The drug substance, and compositions containing it, should preferably be capable of being effectively stored over appreciable periods of time, without exhibiting a

significant change in the active component's physico-chemical characteristics (e.g. its chemical composition, density, hygroscopicity and solubility).

Moreover, it is also important to be able to provide drug in a form which is as chemically pure
5 as possible.

The skilled person will appreciate that, typically, if a drug can be readily obtained in a stable form, such as a stable crystalline form, advantages may be provided, in terms of ease of handling, ease of preparation of suitable pharmaceutical formulations, and a more reliable
10 solubility profile.

Description of the invention

The present invention provides a compound selected from one or more of the following:

- 15
a (1*R*,2*S*)-2-hydroxyindan-1-amine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid;
an L-arginine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxyphenyl)propanoic acid;
20 a *tert*-butylamine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxyphenyl)propanoic acid;
a choline salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid;
or
25 a tris(hydroxymethyl)methylamine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid.

We have found that certain compounds of the invention have the advantage that they may be prepared in crystalline form.

30
According to a further aspect of the invention there is provided a compound of the invention in substantially crystalline form.

Although we have found that it is possible to produce compounds of the invention in forms which are greater than 80% crystalline, by "substantially crystalline" we include greater than 20%, preferably greater than 30%, and more preferably greater than 40% (e.g. greater than any of 50, 60, 70, 80 or 90%) crystalline.

According to a further aspect of the invention there is also provided a compound of the invention in partially crystalline form. By "partially crystalline" we include 5% or between 5% and 20% crystalline.

10 The degree (%) of crystallinity may be determined by the skilled person using X-ray powder diffraction (XRPD). Other techniques, such as solid state NMR, FT-IR, Raman spectroscopy, differential scanning calorimetry (DSC) and microcalorimetry, may also be used.

Compounds of the invention, and particularly crystalline compounds of the invention, may
15 have improved stability when compared to compounds disclosed in PCT/GB02/05743.

The term "stability" as defined herein includes chemical stability and solid state stability.

By "chemical stability", we include that it may be possible to store compounds of the
20 invention in an isolated form, or in the form of a formulation in which it is provided in admixture with pharmaceutically acceptable carriers, diluents or adjuvants (e.g. in an oral dosage form, such as a tablet, capsule etc.), under normal storage conditions, with an insignificant degree of chemical degradation or decomposition.

25 By "solid state stability", we include that it may be possible to store compounds of the invention in an isolated solid form, or in the form of a solid formulation in which it is provided in admixture with pharmaceutically acceptable carriers, diluents or adjuvants (e.g. in an oral dosage form, such as a tablet, capsule etc.), under normal storage conditions, with an insignificant degree of solid state transformation (e.g. crystallisation, recrystallisation, solid
30 state phase transition, hydration, dehydration, solvation or desolvation).

Examples of "normal storage conditions" include temperatures of between minus 80 and plus 50°C (preferably between 0 and 40°C and more preferably room temperatures, such as 15 to

30°C), pressures of between 0.1 and 2 bars (preferably at atmospheric pressure), relative humidities of between 5 and 95% (preferably 10 to 60%), and/or exposure to 460 lux of UV/visible light, for prolonged periods (i.e. greater than or equal to six months). Under such conditions, compounds of the invention may be found to be less than 15%, more preferably less than 10%, and especially less than 5%, chemically degraded/decomposed, or solid state transformed, as appropriate. The skilled person will appreciate that the above-mentioned upper and lower limits for temperature, pressure and relative humidity represent extremes of normal storage conditions, and that certain combinations of these extremes will not be experienced during normal storage (e.g. a temperature of 50°C and a pressure of 0.1 bar).

It may be possible to crystallise salts of compounds of formula A with or without the presence of a solvent system (e.g. crystallisation may be from a melt, under supercritical conditions, or achieved by sublimation). However, we prefer that crystallisation occurs from an appropriate solvent system.

According to a further aspect of the invention, there is provided a process for the preparation of a crystalline compound of the invention which comprises crystallising a compound of the invention from an appropriate solvent system.

Crystallisation temperatures and crystallisation times depend upon the salt that is to be crystallised, the concentration of that salt in solution, and the solvent system which is used.

Crystallisation may also be initiated and/or effected by way of standard techniques, for example with or without seeding with crystals of the appropriate crystalline compound of the invention.

Different crystalline forms of the compounds of the invention may be readily characterised using X-ray powder diffraction (XRPD) methods, for example as described hereinafter.

In order to ensure that a particular crystalline form is prepared in the absence of other crystalline forms, crystallisations are preferably carried out by seeding with nuclei and/or seed crystals of the desired crystalline form in substantially complete absence of nuclei and/or seed crystals of other crystalline forms. Seed crystals of appropriate compound may be prepared,

for example, by way of slow evaporation of solvent from a portion of solution of appropriate salt.

Compounds of the invention may be isolated using techniques which are well known to those skilled in the art, for example decanting, filtering or centrifuging.

Compounds may be dried using standard techniques.

Further purification of compounds of the invention may be effected using techniques, which are well known to those skilled in the art. For example impurities may be removed by way of recrystallisation from an appropriate solvent system. Suitable temperatures and times for the recrystallisation depend upon the concentration of the salt in solution, and upon the solvent system which is used.

When compounds of the invention are crystallised, or recrystallised, as described herein, the resultant salt may be in a form which has improved chemical and/or solid state stability, as mentioned hereinbefore.

Compounds of the invention have the advantage that they may be more efficacious, be less toxic, be longer acting, have a broader range of activity, be more potent, produce fewer side effects, be more easily absorbed, and/or have a better pharmacokinetic profile (e.g. higher oral bioavailability and/or lower clearance), than, and/or have other useful pharmacological, physical, or chemical, properties over, compounds known in the prior art. Compounds of the invention may have the further advantage that they may be administered less frequently than compounds known in the prior art.

Compounds of the invention may also have the advantage that they are in a form which provides for improved ease of handling. Further, compounds of the invention have the advantage that they may be produced in forms which may have improved chemical and/or solid state stability (including e.g. due to lower hygroscopicity). Thus, such compounds of the invention may be stable when stored over prolonged periods.

Compounds of the invention may also have the advantage that they may be crystallised in good yields, in a high purity, rapidly, conveniently, and at a low cost.

The compounds of the present invention have activity as medicaments. In particular the
5 compounds are highly potent agonists of PPAR α . In addition the compounds are also agonists of PPAR γ . The term agonists as used herein, includes partial agonists.

It will also be understood that certain crystalline compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It is to be understood
10 that the present invention encompasses all such solvated and unsolvated forms.

The present invention also provides the following embodiments.

A (1*R*,2*S*)-2-hydroxyindan-1-amine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid characterised by an X-ray powder
15 diffraction pattern characterised by peaks with d-values at 20.0, 11.0, 6.5, 4.41, 4.04 and 3.90 Å.

A (1*R*,2*S*)-2-hydroxyindan-1-amine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid having the XRPD pattern substantially as disclosed in figure
20 A.

A *tert*-butylamine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxyphenyl)propanoic acid characterised by an X-ray powder diffraction pattern
25 characterised by peaks with d-values at 18.7, 11.5, 5.9, 5.5, 4.71 and 4.08 Å.

A *tert*-butylamine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxyphenyl)propanoic acid having the XRPD pattern substantially as disclosed in figure
B.

30 Methods of preparation

The compounds of the invention are prepared by dissolving (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid in an inert solvent at a temperature in

the range of 0-100°C and then adding the appropriate amine either neat or as a solution in an inert solvent and isolating the solid salt. The salt may be isolated by cooling the reaction solution and optionally seeding the solution with the desired product and/or concentrating the solution. Optionally the product may be isolated by adding an antisolvent to a solution of the product in an inert solvent. The solid may be collected by methods known to those skilled in the art for example filtration or centrifugation.

In another aspect the present invention provides the compound obtainable by reacting (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid and *tert*-butylamine in an inert solvent, particularly acetone and isolating the product. Particularly an equivalent of *tert*-butylamine is used.

In another aspect the present invention provides the compound obtainable by reacting (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid and (1*R*,2*S*)-2-hydroxyindan-1-amine in an inert solvent, particularly ethyl acetate and isolating the product. Particularly an equivalent of (1*R*,2*S*)-2-hydroxyindan-1-amine is used.

In another aspect the present invention provides the compound obtainable by reacting (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid and (1*R*,2*S*)-2-hydroxyindan-1-amine in an inert solvent, particularly ethyl acetate or isopropyl acetate, and isolating the product. Particularly an equivalent of (1*R*,2*S*)-2-hydroxyindan-1-amine is used.

In another aspect the present invention provides the compound obtainable by reacting (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid and L-arginine in an inert solvent, particularly ethanol or propan-2-ol and isolating the product. Particularly an equivalent of L-arginine is used.

In another aspect the present invention provides the compound obtainable by reacting (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid and choline in an inert solvent and isolating the product. Particularly an equivalent of choline is used.

In another aspect the present invention provides the compound obtainable by reacting (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid and tris(hydroxymethyl)methylamine and isolating the product. Particularly an equivalent of
5 tris(hydroxymethyl)methylamine is used.

The expression "inert solvent" refers to a solvent that does not react with the starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

Pharmaceutical preparations

The compounds of the invention will normally be administered via the oral, parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal, rectal, vaginal,
15 transdermal and/or nasal route and/or via inhalation, in the form of pharmaceutical preparations in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

20 Suitable daily doses of the compound of the invention in therapeutical treatment of humans are about 0.0001-100 mg/kg body weight, preferably 0.001-10 mg/kg body weight.

Oral formulations are preferred particularly tablets or capsules which may be formulated by methods known to those skilled in the art to provide doses of the active compound in the
25 range of 0.5mg to 500mg for example 1 mg, 3 mg, 5 mg, 10 mg, 25mg, 50mg, 100mg and 250mg.

According to a further aspect of the invention there is thus provided a pharmaceutical formulation including the compound of the invention in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

Pharmacological properties

The compounds of the invention are useful for the prophylaxis and/or treatment of clinical conditions associated with inherent or induced reduced sensitivity to insulin (insulin resistance) and associated metabolic disorders (also known as metabolic syndrome). These clinical conditions will include, but will not be limited to, general obesity, abdominal obesity, 5 arterial hypertension, hyperinsulinaemia, hyperglycaemia, type 2 diabetes and the dyslipidaemia characteristically appearing with insulin resistance. This dyslipidaemia, also known as the atherogenic lipoprotein profile, is characterised by moderately elevated non-esterified fatty acids, elevated very low density lipoprotein (VLDL) triglyceride rich particles, high Apo B levels, low high density lipoprotein (HDL) levels associated with low apoAI 10 particle levels and high Apo B levels in the presence of small, dense, low density lipoproteins (LDL) particles, phenotype B.

The compounds of the present invention are expected to be useful in treating patients with combined or mixed hyperlipidemias or various degrees of hypertriglyceridemias and 15 postprandial dyslipidemia with or without other manifestations of the metabolic syndrome. Treatment with the present compounds is expected to lower the cardiovascular morbidity and mortality associated with atherosclerosis due to their antidyslipidaemic as well as antiinflammatory properties. The cardiovascular disease conditions include macro-angiopathies of various internal organs causing myocardial infarction, congestive heart 20 failure, cerebrovascular disease and peripheral arterial insufficiency of the lower extremities. Because of its insulin sensitizing effect the compound is also expected to prevent or delay the development of type 2 diabetes from the metabolic syndrome and diabetes of pregnancy. Therefore the development of long-term complications associated with chronic hyperglycaemia in diabetes mellitus such as the micro-angiopathies causing renal disease, 25 retinal damage and peripheral vascular disease of the lower limbs are expected to be delayed. Furthermore the compound may be useful in treatment of various conditions outside the cardiovascular system whether or not associated with insulin resistance, like polycystic ovarian syndrome, obesity, cancer and states of inflammatory disease including neurodegenerative disorders such as mild cognitive impairment, Alzheimer's disease, 30 Parkinson's disease and multiple sclerosis.

The compounds of the present invention are expected to be useful in controlling glucose levels in patients suffering from type 2 diabetes.

The present invention provides a method of treating or preventing dyslipidemias, the insulin resistance syndrome and/or metabolic disorders (as defined above) comprising the administration of a compound of the present invention to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating or preventing type 2 diabetes comprising the administration of an effective amount of a compound of the present invention to a mammal (particularly a human) in need thereof.

In a further aspect the present invention provides the use of a compound of the present invention as a medicament.

In a further aspect the present invention provides the use of a compound of the present invention in the manufacture of a medicament for the treatment of insulin resistance and/or metabolic disorders.

Combination Therapy

The compounds of the invention may be combined with another therapeutic agent that is useful in the treatment of disorders associated with the development and progress of atherosclerosis such as hypertension, hyperlipidaemias, dyslipidaemias, diabetes and obesity. The compound of the invention may be combined with another therapeutic agent that decreases the ratio of LDL:HDL or an agent that causes a decrease in circulating levels of LDL-cholesterol. In patients with diabetes mellitus the compound of the invention may also be combined with therapeutic agents used to treat complications related to micro-angiopathies.

A compound of the invention may be used alongside other therapies for the treatment of metabolic syndrome or type 2 diabetes and its associated complications, these include biguanide drugs, for example metformin, phenformin and buformin, insulin (synthetic insulin analogues, amylin) and oral antihyperglycemics (these are divided into prandial glucose regulators and alpha-glucosidase inhibitors). An example of an alpha-glucosidase inhibitor is acarbose or voglibose or miglitol. An example of a prandial glucose regulator is repaglinide or

nateglinide.

In another aspect of the invention, a compound of the invention may be administered in association with another PPAR modulating agent. PPAR modulating agents include but are not limited to a PPAR alpha and/or gamma and /or delta agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable PPAR alpha and/or gamma agonists, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are well known in the art. These include the compounds described in WO 01/12187, WO 01/12612, WO 99/62870, WO 99/62872, WO 99/62871, WO 98/57941, WO 01/40170, J Med Chem, 1996, 39, 665, Expert Opinion on Therapeutic Patents, 10 (5), 623-634 (in particular the compounds described in the patent applications listed on page 634) and J Med Chem, 2000, 43, 527 which are all incorporated herein by reference. Particularly a PPAR alpha and/or gamma agonist refers to BMS 298585, clofibrate, fenofibrate, bezafibrate, gemfibrozil and ciprofibrate; GW 9578, pioglitazone, rosiglitazone, rivoglitazone, balaglitazone, KRP-297, JTT-501, SB 213068, GW 1929, GW 7845, GW 0207, L-796449, L-165041 and GW 2433. Particularly a PPAR alpha and/or gamma agonist refers to (S)-2-ethoxy-3-[4-(2-{4-methanesulphonyloxy-phenyl}ethoxy)phenyl]propanoic acid and pharmaceutically acceptable salts thereof.

In addition a compound of the invention may be used in conjunction with a sulfonylurea for example: glimepiride, glibenclamide (glyburide), gliclazide, glipizide, gliquidone, chlorpropamide, tolbutamide, acetohexamide, glycopyramide, carbutamide, glibonuride, glisoxepid, glybuthiazole, glibuzole, glyhexamide, glymidine, glypinamide, phenbutamide, tolcyclamide and tolazamide. Preferably the sulfonylurea is glimepiride or glibenclamide (glyburide). More preferably the sulfonylurea is glimepiride. The present invention includes administration of a compound of the present invention in conjunction with one, two or more existing therapies described in this combination section. The doses of the other existing therapies for the treatment of type 2 diabetes and its associated complications will be those known in the art and approved for use by regulatory bodies for example the FDA and may be found in the Orange Book published by the FDA. Alternatively smaller doses may be used as a result of the benefits derived from the combination. The present invention also includes a compound of the present invention in combination with a cholesterol-lowering agent. The cholesterol-lowering agents referred to in this application include but are not limited to

inhibitors of HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A reductase).

Suitably the HMG-CoA reductase inhibitor is a statin selected from the group consisting of atorvastatin, bervastatin, cerivastatin, dalvastatin, fluvastatin, itavastatin, lovastatin, mevastatin, nicostatin, nivastatin, pravastatin and simvastatin, or a pharmaceutically

5 acceptable salt, especially sodium or calcium, or a solvate thereof, or a solvate of such a salt.

A particular statin is atorvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A more particular statin is atorvastatin calcium salt. A

particularly preferred statin is, however, a compound with the chemical name (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)-amino]-pyrimidin-5-yl](3R,5S)-3,5-

10 dihydroxyhept-6-enoic acid, [also known as (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[N-methyl-N-(methylsulfonyl)-amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid]

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt. The

compound (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl-(methylsulfonyl)-amino]-

pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid, and its calcium and sodium salts are

15 disclosed in European Patent Application, Publication No. EP-A-0521471, and in Bioorganic and Medicinal Chemistry, (1997), 5(2), 437-444. This latter statin is now known under its generic name rosuvastatin.

In the present application, the term "cholesterol-lowering agent" also includes chemical

20 modifications of the HMG-CoA reductase inhibitors, such as esters, prodrugs and metabolites, whether active or inactive.

The present invention also includes a compound of the present invention in combination with a bile acid sequestering agent, for example colestipol or cholestyramine or cholestagel.

25

The present invention also includes a compound of the present invention in combination with an inhibitor of the ileal bile acid transport system (IBAT inhibitor).

Suitable compounds possessing IBAT inhibitory activity have been described, see for instance

30 the compounds described in WO 93/16055, WO 94/18183, WO 94/18184, WO 96/05188, WO 96/08484, WO 96/16051, WO 97/33882, WO 98/07449, WO 98/03818, WO 98/38182, WO 99/32478, WO 99/35135, WO 98/40375, WO 99/35153, WO 99/64409, WO 99/64410, WO 00/01687, WO 00/47568, WO 00/61568, WO 00/62810, WO 01/68906, DE 19825804,

WO 00/38725, WO 00/38726, WO 00/38727, WO 00/38728, WO 00/38729, WO 01/68906, WO 01/66533, WO 02/32428, WO 02/50051, EP 864 582, EP489423, EP549967, EP573848, EP624593, EP624594, EP624595 and EP624596 and the contents of these patent applications are incorporated herein by reference.

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Particular classes of IBAT inhibitors suitable for use in the present invention are benzothiepinines, and the compounds described in the claims, particularly claim 1, of WO 00/01687, WO 96/08484 and WO 97/33882 are incorporated herein by reference. Other suitable classes of IBAT inhibitors are the 1,2-benzothiazepines, 1,4-benzothiazepines and 1,5-benzothiazepines. A further suitable class of IBAT inhibitors is the 1,2,5-benzothiadiazepines.

One particular suitable compound possessing IBAT inhibitory activity is (3*R*,5*R*)-3-butyl-3-ethyl-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,4-benzothiazepin-8-yl \square -D-glucopyranosiduronic acid (EP 864 582). Other suitable IBAT inhibitors include one of:

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(carboxymethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N'*-(carboxymethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(2-sulphoethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(2-sulphoethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N'*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N'*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N'*-(2-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N'*-(2-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N'*-(5-carboxypentyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N'*-(2-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{ α -[*N'*-(2-sulphoethyl)carbamoyl]-2-fluorobenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 5 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N'*-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N'*-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)- α -(*N'*-{(R)-1-[*N''*-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl]-2-hydroxyethyl}carbamoyl)benzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 10 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{ α -[*N'*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{ α -[*N'*-(ethoxy)(methyl)phosphorylmethyl]carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 15 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-{*N*-[(R)- α -(*N'*-{2-[(hydroxy)(methyl)phosphoryl]ethyl}carbamoyl)benzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N'*-(2-methylthio-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 20 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)- α -(*N'*-{2-[(methyl)(ethyl)phosphoryl]ethyl}carbamoyl)-4-hydroxybenzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)- α -(*N'*-{2-[(methyl)(hydroxy)phosphoryl]ethyl}carbamoyl)-4-hydroxybenzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 25 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[(R)-*N'*-(2-methylsulphinyl)-1-carboxyethyl]carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methoxy-8-[*N*-{(R)- α -[*N'*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 30

- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-((R)-1-carboxy-2-methylthioethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-((S)-1-carboxybutyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-((S)-1-carboxypropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-((S)-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-((S)-1-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-((R)-1-carboxy-2-methylthioethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-{(S)-1-[*N*-((S)-2-hydroxy-1-carboxyethyl)carbamoyl]propyl}carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-((S)-1-carboxypropyl) carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-((R/S)- α -{*N*-[1-(R)-2-(S)-1-hydroxy-1-(3,4-dihydroxyphenyl)prop-2-yl] carbamoyl}-4-hydroxybenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl) carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; and

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl) carbamoyl]benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the present invention the formula A optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration one or more of the following agents selected from:

a CETP (cholesteryl ester transfer protein) inhibitor, for example those referenced and described in WO 00/38725 page 7 line 22 - page 10, line 17 which are incorporated herein by reference;

a cholesterol absorption antagonist for example azetidinones such as SCH 58235 and those described in US 5,767,115 which are incorporated herein by reference;

a MTP (microsomal transfer protein) inhibitor for example those described in Science, 282, 751-54, 1998 which are incorporated herein by reference;

a nicotinic acid derivative, including slow release and combination products, for example, nicotinic acid (niacin), acipimox and niceritrol;

a phytosterol compound for example stanols;

probucol;

an omega-3 fatty acid for example OmacorTM;

an anti-obesity compound for example orlistat (EP 129,748) and sibutramine (GB 2,184,122 and US 4,929,629);

- an antihypertensive compound for example an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an adrenergic blocker, an alpha adrenergic blocker, a beta adrenergic blocker for example metoprolol, a mixed alpha/beta adrenergic blocker, an adrenergic stimulant, calcium channel blocker, an AT-1 blocker, a saluretic, a diuretic or a vasodilator;
- a CB1 antagonist or inverse agonist for example as described in WO01/70700 and EP 65635 ; aspirin;
- a Melanin concentrating hormone (MCH) antagonist;
- a PDK inhibitor; or
- modulators of nuclear receptors for example LXR, FXR, RXR, and RORalpha;
- or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.
- Particular ACE inhibitors or pharmaceutically acceptable salts, solvates, solvate of such salts or a prodrugs thereof, including active metabolites, which can be used in combination with a compound of the invention include but are not limited to, the following compounds: alacepril, alatripril, altiopril calcium, ancovenin, benazepril, benazepril hydrochloride, benazeprilat, benzoylcaptopril, captopril, captopril-cysteine, captopril-glutathione, ceranapril, ceranopril, ceronapril, cilazapril, cilazaprilat, delapril, delapril-diacid, enalapril, enalaprilat, enapril, epicaptopril, foroxymithine, fosfenopril, fosenopril, fosenopril sodium, fosinopril, fosinopril sodium, fosinoprilat, fosinoprilic acid, glycopril, hemorphin-4, idrapril, imidapril, indolapril, indolaprilat, libenzapril, lisinopril, lyciumin A, lyciumin B, mixanpril, moexipril, moexiprilat, moveltipril, muracein A, muracein B, muracein C, pentopril, perindopril, perindoprilat, pivalopril, pivopril, quinapril, quinapril hydrochloride, quinaprilat, ramipril, ramiprilat, spirapril, spirapril hydrochloride, spiraprilat, spiropril, spiropril hydrochloride, temocapril, temocapril hydrochloride, teprotide, trandolapril, trandolaprilat, utibapril, zabicipril, zabiciprilat, zofenopril and zofenoprilat. Preferred ACE inhibitors for use in the present invention are ramipril, ramiprilat, lisinopril, enalapril and enalaprilat. More preferred ACE inhibitors for uses in the present invention are ramipril and ramiprilat.
- Preferred angiotensin II antagonists, pharmaceutically acceptable salts, solvates, solvate of such salts or a prodrugs thereof for use in combination with a compound of the invention include, but are not limited to, compounds: candesartan, candesartan cilexetil, losartan,

valsartan, irbesartan, tasosartan, telmisartan and eprosartan. Particularly preferred angiotensin II antagonists or pharmaceutically acceptable derivatives thereof for use in the present invention are candesartan and candesartan cilexetil.

5 Therefore in an additional feature of the invention, there is provided a method for for the treatment of type 2 diabetes and its associated complications in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of the present invention in simultaneous, sequential or separate administration with an effective amount of one the other compounds described in this
10 combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment
15 which comprises administering to said animal an effective amount of a compound of the present invention of a compound of the invention in simultaneous, sequential or separate administration with an effective amount of one the other compounds described in this combination section or a pharmaceutically acceptable salt; solvate, solvate of such a salt or a prodrug thereof.

20 According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the present invention and one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or
25 carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of the present invention and one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a
30 prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising:
a) a compound of the present invention in a first unit dosage form;

b) one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

5

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of the present invention together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;

b) one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the present invention and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of metabolic syndrome or type 2 diabetes and its associated complications in a warm-blooded animal, such as man.

20

According to another feature of the invention there is provided the use of a compound of the present invention and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the present invention optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a

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pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Experimental

¹H NMR and ¹³C NMR measurements were performed on a Varian Mercury 300 or Varian UNITY plus 400, 500 or 600 spectrometers, operating at ¹H frequencies of 300, 400, 500 and 600 MHz, respectively, and at ¹³C frequencies of 75, 100, 125 and 150 MHz, respectively. Measurements were made on the delta scale (δ).

Unless otherwise stated, chemical shifts are given in ppm with the solvent as internal standard.

X-ray powder diffraction analysis (XRPD) was performed using variable slits on samples prepared according to standard methods with and/or without using an internal standard.

Standard methods are, for example described in Giacobazzo, C. *et al* (1995), *Fundamentals of Crystallography*, Oxford University Press; Jenkins, R. and Snyder, R. L. (1996), *Introduction to X-Ray Powder Diffractometry*, John Wiley & Sons, New York; Bunn, C. W. (1948), *Chemical Crystallography*, Clarendon Press, London; or Klug, H. P. & Alexander, L. E. (1974), *X-ray Diffraction Procedures*, John Wiley and Sons, New York. X-ray analyses were performed using a Siemens D5000 diffractometer or a Philips X'Pert MPD. . X-ray analyses were performed using Cu-radiation a Siemens D5000 diffractometer and a Philips X'Pert MPD. The X-axis in the figures below is 2-theta and the Y axis is intensity.

Differential scanning calorimetry (DSC) was performed using a Mettler DSC820, a Mettler DSC820E or a Perkin Elmer DSC 7 instrument, according to standard methods, for example those described in Höhne, G. W. H. *et al* (1996), *Differential Scanning Calorimetry*, Springer, Berlin.

Thermogravimetric analysis (TGA) was performed using a Mettler Toledo TGA850, a Mettler Toledo TG851 or a Perkin Elmer TGA 7 instrument.

It will be appreciated by the skilled person that crystalline forms of compounds of the invention may be prepared by analogy with processes described herein and/or in accordance



with the Examples below, and may show essentially the same XRPD diffraction patterns and/or DSC and/or TGA thermograms as those disclosed herein. By “essentially the same” XRPD diffraction patterns and/or DSC and/or TGA thermograms, we include those instances when it is clear from the relevant patterns and/or thermograms (allowing for experimental error) that essentially the same crystalline form has been formed. When provided, DSC onset temperatures may vary in the range $\pm 5^{\circ}\text{C}$ (e.g. $\pm 2^{\circ}\text{C}$), and XRPD distance values may vary in the range ± 2 on the last decimal place. It will be appreciated by the skilled person that XRPD intensities may vary when measured for essentially the same crystalline form for a variety of reasons including, for example, preferred orientation.

Abbreviations

DMSO	dimethyl sulfoxide
THF	tetrahydrofuran
Pd/C	palladium on charcoal
15 DMAP	dimethylaminopyridine
t	triplet
s	singlet
d	doublet
q	quartet
20 m	multiplet
bs	broad singlet
dm	doublet of multiplet
bt	broad triplet
dd	doublet of doublet
25 XRPD	X-ray powder diffraction
TGA	thermogravimetric analysis
DSC	differential scanning calorimetry

ExamplesPreparation of Starting MaterialMethod 15 (2S)-2-Ethoxy-3-(4-[2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy]phenyl)propanoic acid(i) Ethyl (2S)-3-[4-[2-(benzyloxy)-2-oxoethoxy]phenyl]-2-ethoxypropanoate

To a solution of ethyl (2S)-2-ethoxy-3-(4-hydroxyphenyl)propanoate (23.8 g, 100 mmol,
10 prepared as described in WO99/62872) in acetonitrile (200 mL) was added anhydrous potassium carbonate (31.9 g, 231 mmol) followed by benzyl bromoacetate (17.4 mL, 110 mmol) and the reaction mixture was refluxed overnight. The reaction mixture was allowed to cool to room temperature, insoluble salts were filtered off and the solution was concentrated *in vacuo*. The residue was taken up in ethyl acetate (300 mL), and the organic phase was washed with aqueous
15 NaHCO₃ (3 x 100 mL) and brine (100 mL), dried over anhydrous MgSO₄, and concentrated *in vacuo*. Purification on silica gel with methylene chloride as the eluent and collection of pure fractions yielded 22.4 g (58%) of a yellow oil.

¹H NMR (400 MHz, CDCl₃): □ 1.16 (t, 3H), 1.22 (t, 3H), 2.93–2.97 (m, 2H), 3.35 (m, 1H), 3.60
20 (m, 1H), 3.97 (m, 1H), 4.16 (q, 2H), 4.64 (s, 2H), 5.23 (s, 2H), 6.82 (d, 2H), 7.15 (d, 2H), 7.32–7.39 (m, 5H).

¹³C NMR (100 MHz, CDCl₃): □ 14.3, 15.2, 38.6, 60.9, 65.6, 66.3, 67.0, 80.4, 114.6, 128.5,
128.6, 128.7, 130.6, 135.3, 156.7, 169.0, 172.6.

25

(ii) {4-[(2S)-2,3-Diethoxy-3-oxopropyl]phenoxy}acetic acid

To a solution of ethyl (2S)-3-[4-[2-(benzyloxy)-2-oxoethoxy]phenyl]-2-ethoxypropanoate (22.33 g, 57.8 mmol) in freshly distilled THF (290 mL) was added Pd/C (10%, 3.1 g) and the
30 reaction mixture was hydrogenated under atmospheric pressure at room temperature overnight. The mixture was filtered through a plug of Celite and the filtrate was concentrated *in vacuo* to afford 16.6 g (97%) of a light yellow oil.

¹H NMR (400 MHz, CDCl₃): □ 1.15 (t, 3H), 1.21 (t, 3H), 2.93–2.98 (m, 2H), 3.35 (m, 1H), 3.60 (m, 1H), 3.97 (m, 1H), 4.16 (q, 2H), 4.65 (s, 2H), 6.84 (d, 2H), 7.17 (d, 2H), 8.48 (bs, 1H)

¹³C NMR (100 MHz, CDCl₃): □ 14.3, 15.1, 38.5, 61.0, 65.1, 66.4, 80.3, 114.6, 130.7, 130.9,
5 156.4, 172.7, 173.7

(iii) Ethyl (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoate

10 To a solution of {4-[(2*S*)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (0.110 g, 0.37 mmol) in methylene chloride (3.7 mL) were added N-hexyl-2-phenylethylamine (0.080 g, 0.39 mmol) and DMAP (0.045 g, 0.37 mmol) followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.071 g, 0.37 mmol), and the reaction mixture was stirred at room temperature overnight. The mixture was diluted with methylene chloride (25 mL), and the organic phase was
15 washed with 5% HCl (3 x 25 mL), aqueous NaHCO₃ (25 mL) and brine (25 mL), dried over Na₂SO₄, and concentrated *in vacuo*. Purification on a prepacked column of silica gel (Isolute® SPE Column, 5 g Si/25 mL) with methanol (0–1% gradient) in methylene chloride as the eluent yielded 0.125 g (70%) of a colourless oil.

20 ¹H NMR (400 MHz, CDCl₃): □ 0.82–0.92 (m, 3H), 1.16 (t, 3H), 1.19–1.33 (m, 9H), 1.45–1.65 (m, 2H), 2.82–2.90 (m, 2H), 2.91–2.98 (m, 2H), 3.12–3.21 and 3.29–3.42 (2m, 3H, rotamers) 3.50–3.65 (m, 3H), 3.95 (m, 1H), 4.16 (q, 2H), 4.39 and 4.65 (2s, 2H, rotamers), 6.75 and 6.86 (2d, 2H, rotamers), 7.10–7.34 (m, 7H).

25 ¹³C NMR (100 MHz, CDCl₃): □ 14.0, 14.1, 14.3, 15.1, 22.6, 26.5, 26.7, 27.4, 29.0, 31.5, 31.6, 33.9, 35.3, 38.5, 45.9, 48.1, 48.3, 48.9, 60.8, 66.2, 67.5, 80.4, 114.5, 126.4, 126.9, 128.5, 128.9, 130.1, 130.2, 130.5, 130.5, 138.3, 139.2, 156.9, 157.0, 167.6, 167.8, 172.5. (The number of peaks is larger than the number of carbon atoms due to rotamers.)

30 (iv) (2*S*)-2-Ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid

To a solution of ethyl (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoate (0.081 g, 0.17 mmol) in THF (8.6 mL) was added 4.3 mL of a

0.10 M LiOH solution and the reaction mixture was stirred at room temperature overnight. The reaction mixture was acidified with 2M HCl and extracted with ethyl acetate (3 x 25mL). The combined organic phase was washed with brine (25 mL), dried over Na₂SO₄, and concentrated *in vacuo* to afford 0.073 g (96%) of a colourless oil.

¹H NMR (400 MHz, CDCl₃): □ 0.82–0.93 (m, 3H), 1.15 (t, 3H), 1.20–1.35 (m, 6H), 1.47–1.62 (m, 2H), 2.80–2.99 (m, 3H), 3.00–3.09 (m, 1H), 3.11–3.21 and 3.31–3.44 (2m, 3H, rotamers), 3.50–3.67 (m, 3H), 4.01 (m, 1H), 4.40 and 4.66 (2s, 2H, rotamers), 6.75 and 6.85 (2d, 2H, rotamers), 7.10–7.35 (m, 7H), 8.86 (bs, 1H).

¹³C NMR (100 MHz, CDCl₃): □ 14.0, 14.1, 15.1, 22.6, 22.6, 26.6, 26.7, 27.3, 28.9, 31.5, 31.6, 33.8, 35.2, 38.1, 46.1, 48.3, 48.4, 49.0, 66.7, 67.4, 79.9, 114.6, 126.4, 127.0, 128.6, 128.9, 130.0, 130.1, 130.6, 130.7, 138.2, 139.1, 156.9, 157.0, 168.1, 168.2, 175.6. (The number of peaks is larger than the number of carbon atoms due to rotamers.)

Method 2

(2S)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid

a) Phenethylamine (50.10g) was treated with sodium hydroxide (53g) in toluene (260.1g) and water (75ml). A solution of chloroacetyl chloride (56.50g) in toluene (78g) was added under temperature control. After complete reaction, the reaction slurry was heated until a complete solution is obtained, and the water-phase was removed. The organic phase was washed once with aqueous hydrogen chloride and once with water. The resulting toluene phase was reduced by evaporation and diisopropylether was added to the toluene solution. The solution was cooled and 1-chloro N-phenethylacetamide (71.0 g) was collected by filtration, washed and dried.

b) A mixture of potassium carbonate (122.36g), 1-chloro N-phenethylacetamide (52.0g), ethyl (2S)-2-ethoxy-3-(4-hydroxyphenyl)propanoate (60.27g) (see WO 99/62871) and acetonitrile (314g) was stirred and brought to the boil under reflux. After complete reaction, the mixture was cooled and the inorganic salts were filtered off and washed with acetonitrile. The remaining solution was reduced by distillation and diisopropyl ether added. The solution is cooled and ethyl (2S)-2-ethoxy-3-(4-{2-oxo-2-[(2-

phenylethyl)amino]ethoxy}phenyl)propanoate (82g) is collected by filtration, washed and dried.

c) A solution of ethyl (2*S*)-2-ethoxy-3-(4-{2-oxo-2-[(2-phenylethyl)amino]ethoxy}-phenyl)propanoate(82.0g) in THF (356g) was added to a solution of lithium hydroxide (14.6g) dissolved in water (600ml) . The mixture was stirred at room temperature. After complete reaction, the mixture was evaporated under reduced pressure to remove THF. After evaporation, the reaction mixture was cooled to room temperature and acidified with hydrochloric acid. The acidified product was extracted with ethyl acetate. The ethyl acetate solution was washed with water and evaporated to a reduced volume. When no more water came off, the residual ethyl acetate solution was diluted with diisopropyl ether to initiate precipitation. (2*S*)-2-Ethoxy-3-(4-{2-oxo-2-[(2-phenylethyl)amino]ethoxy}phenyl)-propanoic acid was filtered off and washed with diisopropyl ether and dried under vacuum.

d) Dimethylsulfoxide (DMSO) (2750 mL), potassium hydroxide powder (244 g) and (2*S*)-2-ethoxy-3-(4-{2-oxo-2-[(2-phenylethyl)amino]ethoxy}phenyl)propanoic acid (250 g) were stirred at approximately 18°C for ca 20 minutes. 1-Bromohexane (344 g = 292 mL) was added over 2.5 hours. The reaction mixture was stirred for approximately 10 minutes. Diisopropyl ether (1000 mL) was added followed by filtration, extraction and separation of the mixture. The DMSO layer was further extracted with diisopropyl ether (2x1000 mL). The DMSO layer was acidified with 4M HCl(aq) (950 mL). Diisopropyl ether (3000 mL) and water (2500 mL) were added followed by extraction. The layers were separated (pH~2 of aq layer) and the diisopropyl ether layer was washed with water (2500 mL). The diisopropyl ether layer was concentrated *in vacuo* to give the title compound as a clear, very viscous oil. Yield 317 g, assay 88.1%, corrected yield 91.1%, LC-purity 97.2%, e.e. 97.8%.

Example 1

(1*R*,2*S*)-2-hydroxyindan-1-amine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid

(2*S*)-2-Ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid (1.51 g) was dissolved in ethyl acetate (15 ml/g) at room temperature. Then (1*R*,2*S*)-(+)-cis-amino-2-indanol (1 mole equiv) was added to the solution, followed by addition of seed. The slurry was stirred at room temperature, and the product (1.89 g) was filtered off to give the title compound which was confirmed with XRPD and NMR.

¹H-NMR (400 MHz, CDCl₃):

7.5 (1H, d), 7.4-7.1 (10H, m), 6.8 (1H, d), 6.6 (1H, d), 6.4 (4H, br s), 4.6 (2H, m), 4.4 (2H, m), 3.9 (1H, m), 3.5 (3H, m), 3.4-3.2 (2H, m), 3.2-3.0 (3H, m), 2.9 (4H, m), 1.5 (2H, br m), 1.3 (6H, br s), 1.1 (3H, m), 0.9 (3H, m).

10

Example 2

(1*R*,2*S*)-2-hydroxyindan-1-amine (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid

(2*S*)-2-Ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid (109 mg) and (1*R*,2*S*)-(+)-cis-1-amino-2-indanol (36 mg) were dissolved in ethyl acetate (1.4 ml) and stirred at room temperature. When a salt had precipitated ethyl acetate was added (3.2 ml). The slurry was stirred at room temperature, filtered and the solids washed with ethyl acetate (1 ml) and dried by suction. The product was confirmed as (1*R*,2*S*)-2-hydroxyindan-1-aminium (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoate with LC and XRPD.

Example 3

(1*R*,2*S*)-2-hydroxyindan-1-amine salt (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid

(2*S*)-2-Ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid (1.00 g) and (1*R*,2*S*)-(+)-cis-1-amino-2-indanol (0.27 g) were dissolved in isopropyl acetate (40 ml) and stirred at room temperature. When a salt had precipitated the slurry was filtered and the solids washed with isopropyl acetate (20 ml) and dried by suction to give 0.97 g of title compound.

Example 4

L-arginine salt (2S)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid

5

L-Arginine, (11.32g) was dissolved in 25 ml of distilled water at 60°C. The warm clear solution of L-arginine in water was added under stirring to a solution of (2S)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid (33g) in 2-propanol (150 ml). The resulting solution was evaporated to an oil which was precipitated by adding 150 ml of isopropyl acetate under stirring. The amorphous salt was filtered off and dried under vacuum at 40°C. The yield was 36g. A small amount of material was dissolved in warm butyl acetate and was re-precipitated by addition of cyclohexane. This material was dried in vacuum at 40°C and used for NMR analysis.

¹H-NMR (400 MHz, MeOD):

15 7.2 (7H, m), 6.9 (1H, d), 6.7 (1H, d), 4.7 (1H, s), 4.4 (1H, s), 3.8 (1H, m), 3.6 (4H, m), 3.4 (1H, t), 3.2 (4H, m), 2.9 (4H, m), 1.9 (2H, m), 1.7 (2H, m), 1.6 (2H, br m), 1.3 (6H, br s), 1.1 (3H, t),
0.9 (3H, t)

20 **Example 5**

L-arginine salt (2S)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid

25 The (2S)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid (0.197 g) was dissolved in 95% ethanol and L-arginine (1 mole equiv) was added to the solution. The solution was stirred at ambient temperature, followed by evaporation to dryness and addition of isooctane (10 ml/g). The slurry was stirred at room temperature, and the product was filtered off and analysed by XRPD.

30 **Example 6**

tert-butylamine salt of (2S)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid

(2*S*)-2-Ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid (0,49 g) and *tert*-butylamine (0,077 g) were mixed in acetone(8 ml/g), followed by addition of isooctane (8 ml/g) and stirred at room temperature. The product (0.36 g) was filtered off and washed with isooctane (4 ml/g) and was dried in room temperature. The product was confirmed with NMR and XRPD.

Properties

Examples of properties of (1*R*,2*S*)-2-hydroxyindan-1-amine (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid
DSC showed an endotherm with an extrapolated onset temperature of 104°C. TGA showed a weight loss of 0 % w/w between 24-75°C. DSC analysis repeated on purer sample may give a higher melting point. Crystals of (1*R*,2*S*)-2-hydroxyindan-1-amine (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid (obtained by way of the example above and/or by other ways) were analyzed by XRPD and the results are tabulated below and are shown in Figure A

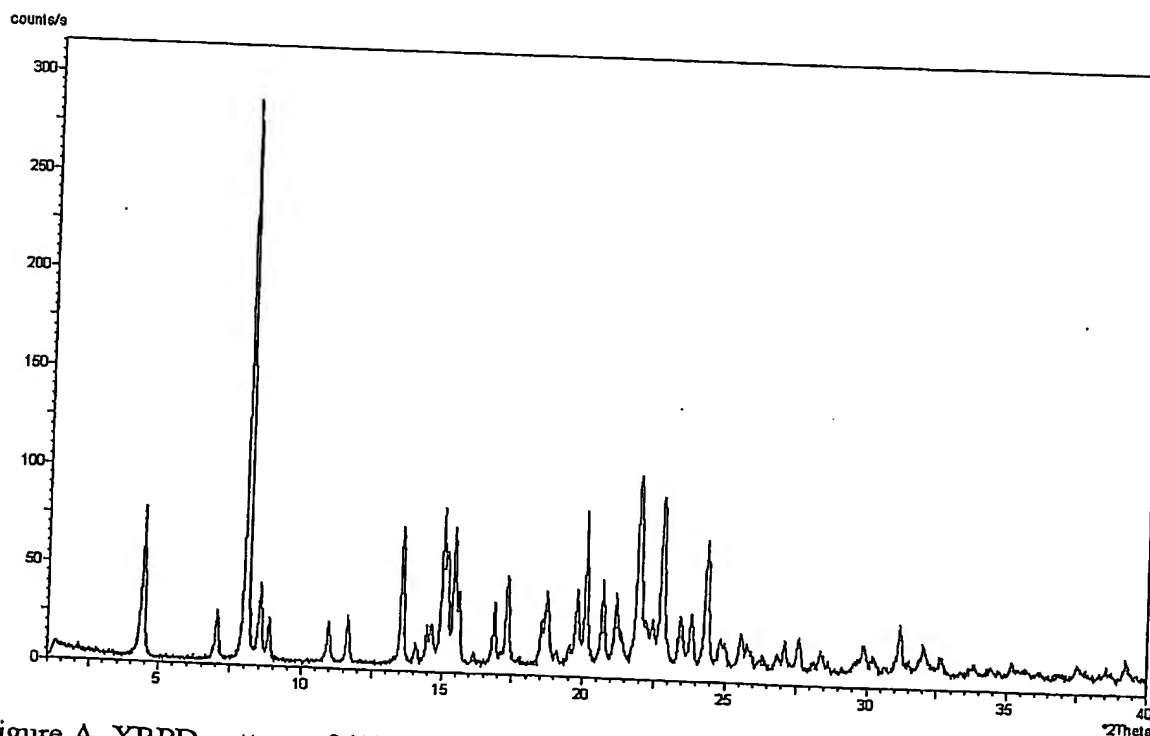


Figure A, XRPD pattern of (1*R*,2*S*)-2-hydroxyindan-1-amine (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid

d-value (Angstrom)	intensity (rel)
20.0	S
12.6	M
11.0	Vs
10.4	M
10.0	M
8.1	m
7.6	m
6.5	s
6.3	w
6.1	m
6.0	m
5.9	s
5.8	s
5.7	s
5.7	m
5.2	m
5.1	s
4.79	m
4.74	m
4.49	m
4.41	s
4.29	m
4.20	m
4.16	w
4.04	s
4.00	w
3.96	m
3.90	s
3.79	m

3.74	m
3.66	s
3.59	w
3.56	w
3.49	w
3.46	w
3.32	w
3.29	w
3.23	w
3.14	w
2.99	w
2.96	w
2.87	m
2.80	w
2.75	w
2.29	w

Examples of properties of *tert*-butylamine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid

5 DSC showed an endotherm with an extrapolated onset temperature of 107°C. TGA showed a weight loss of 12.7% w/w between 102-236°C. DSC analysis repeated on purer sample may give a higher melting point. Crystals of *tert*-butylamine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid (obtained by way of the example above and/or by other ways) were analyzed by XRPD and the results are tabulated
10 below and are shown in Figure B

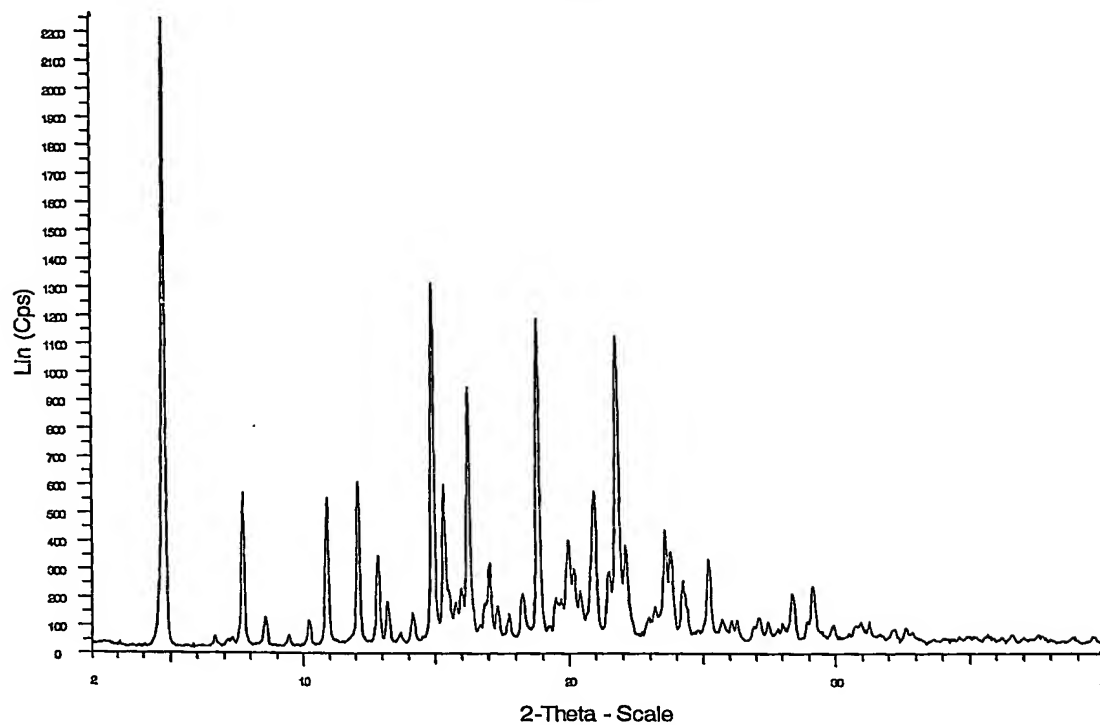


Figure B, XRPD pattern of *tert*-butylamine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid

d-value (Angstrom)	intensity (rel)
18.7	vs
11.5	m
10.4	w
8.7	w
8.1	m
7.3	m
6.9	m
6.7	w
6.3	w
5.9	s
5.8	m
5.5	s
5.2	w
5.1	w

5.00	w
4.86	w
4.71	s
4.44	w
4.24	m
4.08	s
4.02	w
3.77	m
3.74	w
3.67	w
3.53	w
3.14	w
3.06	w

BIOLOGICAL ACTIVITY

Formulations

Compounds were dissolved in DMSO to obtain 16 mM stock solutions. Before assays, stock solutions were further diluted in DMSO and culture media.

GENERAL CHEMICALS AND REAGENTS

Luciferase assay reagent was purchased from Packard, USA. Restriction Enzymes were from Boehringer and Vent polymerase from New England Biolabs.

10 CELL LINES AND CELL CULTURE CONDITIONS

U2-OS, (Osteogenic sarcoma, Human) was purchased from ATCC, USA. Cells were expanded and refrozen in batches from passage number six. Cells were cultured in Dulbecco's modified Eagle medium (DMEM) with 25 mM glucose, 2 mM glutamine or 4 mM L-alanyl-L-glutamine, 10% fetal calf serum, at 5% CO₂. Phosphate buffered saline (PBS) without addition of calcium or magnesium was used. All cell culture reagents were from Gibco (USA) and 96-well cell culture plates were purchased from Wallach.

PLASMID CONSTRUCTS FOR HETEROLOGOUS EXPRESSION

Standard recombinant DNA techniques were carried out as described by Ausubel (7). The Luciferase reporter vector, pGL5UAS (clone consists of five copies of the GAL4 DNA binding sequence, 5'-CGACGGAGTACTGTCCTCCGAGCT-3', cloned into the SacI/XhoI sites of pGL3-Promoter (Promega). The SacI/XhoI fragment carrying the UAS sites was constructed using annealed overlapping oligonucleotides.

Expression vectors used are based upon pSG5 (Stratagene). All vectors contain an EcoRI/NheI fragment encoding the DNA binding domain of GAL4 (encoding amino acid positions 1-145 of database accession number P04386) followed by an in-frame fusion to a fragment encoding the nuclear localisation sequence from T antigen of Polyoma Virus. The nuclear localisation sequence was constructed using annealed overlapping oligonucleotides creating NheI/KpnI sticky ends (5'-CTAGCGCTCCTAGAAGAAACGCAAGGTTGGTAC-3'). The ligand binding domains from human and mouse PPAR α and human and mouse PPAR γ were PCR amplified as KpnI/BamHI fragments and cloned in frame to the GAL4 DNA binding domain and the nuclear localisation sequence. The sequence of all plasmid constructs used were confirmed by sequencing. The following expression vectors were used for transient transfections:

vector	encoded PPAR subtype	sequence reference ¹
pSGGALhPPa	human PPAR α	S74349, nt 625-1530
pSGGALmPPa	murine PPAR α	X57638, nt 668-1573
pSGGALhPPg	human PPAR γ	U63415, nt 613-1518
pSGGALmPPg	murine PPAR γ	U09138, nt 652-1577

¹ refers to nucleotide positions of data base entry used to express the ligand binding domain.

TRANSIENT TRANSFECTIONS

Frozen stocks of cells from passage number six were thawed and expanded to passage number eight before transfections. Confluent cells were trypsinised, washed and pelleted by

centrifugation at 270xg for 2 minutes. The cell pellet was resuspended in cold PBS to a cell concentration of about 18×10^6 cells/ml. After addition of DNA, the cell suspension was incubated on ice for approximately 5 minutes before electroporation at 230 V, 960 μ F in Biorad's Gene PulserTM in 0.5 ml batches. A total of 50 μ g DNA was added to each batch of 0.5 ml cells, including 2.5 μ g expression vector, 25 μ g reporter vector and 22.5 μ g unspecific DNA (pBluescript, Stratagene).

After electroporation, cells were diluted to a concentration of 320'000 cells/ml in DMEM without phenol red, and approximately 25'000 cells/well were seeded in 96-well plates. In order to allow cells to recover, seeded plates were incubated at 37°C for 3-4 hours before addition of test compounds. In assays for PPAR α , the cell medium was supplemented with resin-charcoal stripped fetal calf serum (FCS) in order to avoid background activation by fatty acid components of the FCS. The resin-charcoal stripped FCS was produced as follows; for 500 ml of heat-inactivated FCS, 10 g charcoal and 25 g Bio-Rad Analytical Grade Anion Exchange Resin 200-400 mesh were added, and the solution was kept on a magnetic stirrer at room temperature over night. The following day, the FCS was centrifuged and the stripping procedure was repeated for 4-6 hours. After the second treatment, the FCS was centrifuged and filter sterilised in order to remove remnants of charcoal and resin.

20 ASSAY PROCEDURE

Stock solutions of compounds in DMSO were diluted in appropriate concentration ranges in master plates. From master plates, compounds were diluted in culture media to obtain test compound solutions for final doses.

After adjustment of the amount of cell medium to 75 μ l in each well, 50 μ l test compound solution was added. Transiently transfected cells were exposed to compounds for about 24 hours before the luciferase detection assay was performed. For luciferase assays, 100 μ l of assay reagent was added manually to each well and plates were left for approximately 20 minutes in order to allow lysis of the cells. After lysis, luciferase activity was measured in a 1420 Multiwell counter, Victor, from Wallach.

Reference compounds

The TZD pioglitazone was used as reference substance for activation of both human and murine PPAR γ . 5,8,11,14-Eicosatetrayonic acid (ETYA) was used as reference substance for human PPAR α .

5 Calculations and analysis

For calculation of EC₅₀ values, a concentration-effect curve was established. Values used were derived from the average of two or three independent measurements (after subtraction of the background average value) and were expressed as the percentage of the maximal activation obtained by the reference compound. Values were plotted against the logarithm of
10 the test compound concentration. EC₅₀ values were estimated by linear intercalation between the data points and calculating the concentration required to achieve 50% of the maximal activation obtained by the reference compound.

The compounds of the present invention have an EC₅₀ of less than 0.5 μ mol/l for PPAR α and
15 preferred compounds have an EC₅₀ of less than 0.05 μ mol/l for PPAR α . The compounds of the present invention are more potent with respect to PPAR α than with respect to PPAR γ . It is believed that this relationship is important with respect to the pharmacological activity of the compounds and to their therapeutic profile.

20 In addition the compounds of the present invention exhibit improved DMPK (Drug Metabolism and Pharmacokinetic) properties, for example they exhibit improved metabolic stability *in vitro*, and also exhibit favourable dose response curves *in vivo*. The compounds also have a promising toxicological profile.

Claims:

1. A compound selected from one or more of the following:
 - a (1*R*,2*S*)-2-hydroxyindan-1-amine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid;
 - an L-arginine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxyphenyl)propanoic acid;
 - a *tert*-butylamine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxyphenyl)propanoic acid;
 - 10 a choline salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid;or
 - 15 a tris(hydroxymethyl)methylamine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid.
2. A compound selected from:
 - a (1*R*,2*S*)-2-hydroxyindan-1-amine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid;
 - an L-arginine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxyphenyl)propanoic acid; or
 - 20 a *tert*-butylamine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxyphenyl)propanoic acid.
3. A salt as claimed in claim 1 or claim 2 which may be a solvate, a hydrate, a mixed
25 solvate/hydrate, an anhydrate or an anhydrate.
4. A salt as claimed in any one of claims 1 to 3 in crystalline or partially crystalline form.

ABSTRACT**Title : Therapeutic Agents**

5

A compound selected from one or more of the following:

a (1*R*,2*S*)-2-hydroxyindan-1-amine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid;

an L-arginine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-

10 oxoethoxyphenyl)propanoic acid;

a *tert*-butylamine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxyphenyl)propanoic acid;

a choline salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid;

15 or

a tris(hydroxymethyl)methylamine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid.